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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,797	VISVADER ET AL.	
	Examiner	Art Unit	
	LEI YAO	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *2,4,6,10-17,21 and 24-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5, 7-9, 18-20, 22, 23, and 40-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Request for Continued Examination

The request filed on 7/24/2008 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10779797 is acceptable, and a RCE has been established. An action on the RCE follows.

Claim 41 is added.

Claims 1-41 are pending.

Claims 2, 4, 6, 10-17, 21, 24-39 have been withdrawn previously for non-elected invention.

Claims 1, 3, 5, 7-9, 18-20, 22, 23, and 40-41, drawn to a method for detecting an aberrant cell or diagnosing the presence of an aberrant cell growth comprising detecting the complex of LMO4- antibody to the extent of monoclonal antibody 16H2 (elected) are under consideration.

Previous final Office Action dated 7/24/2007

The rejections in the previous Office action dated 7/24/2007 including rejection of claims under *35 USC § 112 1st paragraph and 35 USC § 102* are withdrawn in view of amendment, applicant's argument and/or new considerations. If any rejection/objection is maintained, it will be stated again below.

Claim Objections

Claim 5 and its depending claims 7-9 are objected to because claim 5 depends any one of claims 1-4, where claims 2 and 4 have been withdrawn from consideration as non-elected invention. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the **second paragraph of 35 U.S.C. 112**:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 depends on claim 1 or 3 and recites the limitation "wherein said immunointeractive molecule" in line 2 of claim 18. There is insufficient antecedent basis for this limitation in the claim because base claim 3 recites only antibody, does not recite a limitation of immunointeractive molecule. Clarification is required.

The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement: claimed method of detecting a complex of LMO4 protein and a mutant or variant of an antibody to LMO4 containing at least one of the CDRs of the variable domain of deimmunized LMO4 antibody.

Claims 3, 5, 7-9, 18, 22-23, and 41are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting an

aberrant cell or a predisposition to the development of mammary cells in a subject by screening the levels of a complex formed between LMO4 protein and an antibody to LMO4 , does not reasonably provide enablement for the method using a mutant or a variant of an antibody that contains at least one of the CDRs of the variable domains derived from the antibodies to LMO4 comprising the antibody 16H2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. .

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988).

To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. The claims are drawn to a method of for detecting an aberrant cell a subject by screening the levels of complex formed between the LMO4 protein or its fragment and an antibody fragment with at least one of the CDRs of the variable domain of the antibody derived from an antibody to LMO4. Thus, all the claims encompass using an antibody mutant or variant, which does not contain a full set of 6 CDRs as evidenced by the recitation f their depending claims 18 and 23.

The specification on page 6, states "invention contemplates a deimmunized antibody molecule having specificity for an epitope recognized by a monoclonal

antibody to LMO4, wherein at least one of the CDRs of the variable domain of said deimmunized antibody is derived from the said monoclonal antibody to LMO4. However, the specification does not provide any working example or any evidence to enable claimed antibody having one of the CDRs specifically binding to LMO4 antigen.

It is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al., (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al., teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma

protein resulted in the loss of antigen-binding function. It is unlikely that deimmunized antibody, thereof as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using a deimmunized antibody, containing fewer than 6 CDRs, resulting in the antibody that retains the antigen specificity of the parental non-human antibody. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed.

Therefore, in view of the lack of guidance in the specification and knowledge in the art one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of using a deimmunized antibody containing at least one of the CDRs.

Applicant is noted that the rejection can be obviated by amending the claims to an antibody containing the full length of a light or a heavy chain or all set of six CDRs if the antibody is a humanized or a chimeric antibody.

Response to applicant's argument:

Applicant on page 14 of the remarks argues:

> that it is simply not necessary that six CDRs necessarily be present in order for a molecule to bind via an immunointeractive mechanism, For example, a single chain antibody will not comprise six CDRs by virtue of the fact that the antibody is a single chain, yet such a molecule will nevertheless bind to LMO4. Further, the three-dimensional structures of antibody and antigen complexes confirm that not all of the six CDRs are necessarily engaged in binding an antigen.

Applicant provides exhibit 7 that shows that antibody to NC-10 only requires 4 CDRs for the antigen binding. In response, first, as discussed above in the rejection one skilled in the art would understand that binding antigen by a fragment of an antibody requires more than one CDR of variable region of the antibody. Whether all of the six CDRs required for the binding of a specific antibody is determined only by experimentation as shown in the reference of exhibit 7. The general rule or experience of skilled artisan has considered that the full length of a light or a heavy chain that including the three CDRs of an antibody is essentially for the antigen binding. However, the modified antibodies, such as humanized or chimeric fragment of an antibody, often require the entire set of six CDRs. As such, if applicant would like to claim an antibody fragment, based on the knowledge of skilled artisan, a full set of six CDRs is required unless experimentation(s) or example(s) presented to allow one skilled in the art to perform the claimed method by using the antibody fragment containing less than a full set of 6 CDRs without undue experimentation.

Applicant further argues:

> in addition to the structural requirement that there be at least one CDR derived from a monoclonal antibody to LMO4, this claim also includes a functional limitation which clearly requires that the antibody is directed to an epitope which is recognized by the LMO4 antibody.

In response, the Office is questioning whether the claimed invention is enabled under requirement of USC 112 1st paragraph. Although the functional language is included in the claims, the specification does not provide the objective evidence that enabling one skilled in the art to make and use the claimed invention of detecting a complex of LMO4 with an antibody fragment containing less than a full set of 6 CDRs of the variant

regions of the antibody. A quantity of experimentation would be enforced before the claimed invention is performed or practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 7-9, 18 -20, 22-23, and 40-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Kenny et al., (PNAS, vol 95, page 11257-11262, 1998, IDS, Feb 04 2005).

Claims are drawn to a method for detecting an aberrant cell or a predisposition to the development of an aberrant cell in a subject or in a biological sample from said subject, said method comprising contacting cells or cell extracts from said subject or said biological sample with an immunointeractive molecule specific to LMO4 comprising an antibody to L-MO4 and elevated presence of said complex relative to a normal cell is indicative of an aberrant cell,

wherein the cells are neoplastic mammary cell or epithelial cell
wherein the immunointeractive molecule is an isolated antibody interacts with LMO4

The immunointeractive molecule encompasses an antibody.

In claims 18, 20 and 23, the method reciting "selected from i, iii, iii,.... is interpreted as selected any one among i, ii, and iii, ...

1. Kenny et al., disclose a method of detecting the levels of LMO4 protein with an antibody to LMO4 by forming a complex in the tissue section by immunohistochemistry (page 11257, col 2 and figure 5, page 11260). The tissue section is biological sample containing a cell.

For this rejection the preamble of detecting an aberrant cell or predisposition to the development of an aberrant cell does not limit the claims because the only active steps in these claims are contacting the biological sample with an immunointeractive molecule or an antibody and screening for the levels of the complex formation (claim 1 and 3). The method of Kenny et al., discloses contacting the tissue section (biological sample) with the antibody to LMO4, HB9 (page 11257, col 2, paragraph) and determining the complex formation by immunohistochemistry (LMO4-antibody), therefore, the reference teaches each and every limitation of the method. For this rejection, the clause "wherein, an elevated presence of the complex related to a normal cells is indicative of an aberrant cell" recited in the claims is not considered as an active method step. The wherein clause is interpreted as a mental step.

2. Claims 1, 3, 5, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Grutz et al., (Oncogene vol 17, page 2799-2803, 1998, IDS, Feb 04 2005).

Claims are set forth above. In this rejection the claims are examined to the full scope of the claimed invention and immunointeractive molecule is interpreted as any binding partner of LMO4 as described in the specification on page 21:

The "immunointeractive molecule" is any molecule having specificity and binding affinity for LM04 or its antigenic parts or its homologues or derivatives.

Grutz et al., disclose NLI1/LDB1 as a Lim-binding protein including LMO4. Grutz et al., disclose a complex formed between LMO4 and NLI1/LDB1 protein. Grutz et al., further disclose that LMO4 is a binding partner of LDB1 (page 2800, col 1).

Conclusion

No claims are allowed.

The method of detecting an aberrant cell by detecting the complex of the LMO4 protein and the antibody secreted by hybridoma 16H2 is free of art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643